

PCT

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INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE
INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation 6 : C07D 405/06, 417/06, 493/04, 313/00, C07C 49/185, 49/17, 59/185, 69/66, C07F 7/18, A61K 31/335, 31/425, 31/44 // (C07D 493/04, 313:00, 303:00)		A3	(11) Internationale Veröffentlichungsnummer: WO 99/07692 (43) Internationales Veröffentlichungsdatum: 18. Februar 1999 (18.02.99)
(21) Internationales Aktenzeichen: PCT/EP98/05064 (22) Internationales Anmeldedatum: 10. August 1998 (10.08.98)		SCHIRNER, Michael [DE/DE]; Eichenstrasse 51, D-13156 Berlin (DE).	
(30) Prioritätsdaten: 197 35 574.9 9. August 1997 (09.08.97) DE 197 35 575.7 9. August 1997 (09.08.97) DE 197 35 578.1 9. August 1997 (09.08.97) DE 197 48 928.1 24. Oktober 1997 (24.10.97) DE 197 49 717.9 31. Oktober 1997 (31.10.97) DE 197 51 200.3 13. November 1997 (13.11.97) DE 198 13 821.0 20. März 1998 (20.03.98) DE		(81) Bestimmungsstaaten: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO Patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(71) Anmelder (<i>für alle Bestimmungsstaaten ausser US</i>): SCHIERING AKTIENGESELLSCHAFT [DE/DE]; Müllerstrasse 178, D-13535 Berlin (DE). (72) Erfinder; und (75) Erfinder/Anmelder (<i>nur für US</i>): KLAR, Ulrich [DE/DE]; Isegrimsteig 8a, D-13503 Berlin (DE). SCHWEDE, Wolfgang [DE/DE]; Klosterheider Weg 35, D-13467 Berlin (DE). SKUBALLA, Werner [DE/DE]; Mittersburger Weg 12, D-13465 Berlin (DE). BUCHMANN, Bernd [DE/DE]; Erdmannstrasse 44, D-16540 Hohen Neuendorf (DE).		Veröffentlicht <i>Mit internationalem Recherchenbericht.</i> <i>Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.</i>	
		(88) Veröffentlichungsdatum des internationalen Recherchenberichts: 14. Mai 1999 (14.05.99)	
(54) Title: NEW EPOTHILONE DERIVATIVES, METHOD FOR PRODUCING SAME AND THEIR PHARMACEUTICAL USE			
(54) Bezeichnung: NEUE EPOTHILON-DERIVATE, VERFAHREN ZU DEREN HERSTELLUNG UND IHRE PHARMAZEUTISCHE VERWENDUNG			
<p style="text-align: center;">(I)</p>			
(57) Abstract			
<p>The invention relates to new epothilone derivatives of the general formula (I), in which the substituents Y, Z, R^{2a}, R^{2b}, R^{4a}, R^{4b}, D-E, R⁵, R⁶, R⁷, R⁸ and X have the meanings assigned to them in the description. The new compounds interact with tubulin by stabilizing formed microtubuli. They are capable of influencing cell division in a phase-specific manner and are suitable for the treatment of malignant tumours, such as ovarian, gastric, colon, breast, lung, head and neck carcinoma, adenocarcinoma, malignant melanoma, and acute lymphocytic and myelocytic leukaemia. They are also suited for anti-angiogenesis therapy and for the treatment of chronic inflammatory diseases (psoriasis, arthritis). To prevent uncontrolled cell growth on, and for better tolerability of, medical implants, the derivatives can be introduced into or applied to polymeric materials. The compounds provided for in the invention can be used alone or, to achieve additive or synergistic effects, in combination with other principles and substance categories used in tumour therapy.</p>			

(57) Zusammenfassung

Die vorliegende Erfindung betrifft die neuen Epothilon-Derivate der allgemeinen Formel (I), worin die Substituenten Y, Z, R^{2a}, R^{2b}, R³, R^{4a}, R^{4b}, D-E, R⁵, R⁶, R⁷, R⁸ und X die in der Beschreibung näher angegebenen Bedeutungen haben. Die neuen Verbindungen interagieren mit Tubulin, indem sie gebildete Mikrotubuli stabilisieren. Sie sind in der Lage, die Zellteilung phasenspezifisch zu beeinflussen und sind zur Behandlung maligner Tumoren geeignet, beispielsweise Ovarial-, Magen-, Colon-, Adeno-, Brust-, Lungen-, Kopf- und Nacken-Karzinome, malignes Melanom, akute lymphozytäre und myelocytäre Leukämie. Außerdem sind sie zur Anti-Angiogenese-Therapie sowie zur Behandlung chronischer entzündlicher Erkrankungen (Psoriasis, Arthritis) geeignet. Zur Vermeidung unkontrollierter Zellwucherungen an sowie der besseren Verträglichkeit von medizinischen Implantaten lassen sie sich in polymere Materialien auf- bzw. einbringen. Die erfindungsgemäßen Verbindungen können alleine oder zur Erzielung additiver oder synergistischer Wirkungen in Kombination mit weiteren in der Tumortherapie anwendbaren Prinzipien und Substanzklassen verwendet werden.

LEDIGLICH ZUR INFORMATION

Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

AL	Albanien	ES	Spanien	LS	Lesotho	SI	Slowenien
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EE	Estland						

INTERNATIONAL SEARCH REPORT

Inter. Application No.
PCT/EP 98/05064

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D405/06	C07D417/06	C07D493/04	C07D313/00	C07C49/185
C07C49/17	C07C59/185	C07C69/66	C07F7/18	A61K31/335
A61K31/425	A61K31/44	//(C07D493/04, 313:00, 303:00)		

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 19086 A (GESELLSCHAFT FÜR BIOTECHNOLOGISCHE FORSCHUNG MBH) 29 May 1997 cited in the application see page 7, last paragraph see claims 4,13 ----	1-7,10, 11
X	DE 41 38 042 A (GESELLSCHAFT FÜR BIOTECHNOLOGISCHE FORSCHUNG MBH) 27 May 1993 see claims 1,2,8 ----	1-7,10, 11 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

9 March 1999

Date of mailing of the international search report

22/03/1999

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

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Hass, C

INTERNATIONAL SEARCH REPORT

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nal Application No
PCT/EP 98/05064

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	K. C. NICOLAOU ET AL.: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 119, no. 34, 1997, pages 7974-91, XP002095719 cited in the application see scheme 1, compounds 1 and 2; scheme 2, compound 20	1-7.13
P,X	K. C. NICOLAOU: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 119, no. 34, 1997, pages 7960-73, XP002064442 cited in the application see page 7960, compounds 1 and 2	1-7
A	see page 7961, scheme 1, compound 8	13
X	---	
D. SCHINZER ET AL.: ANGEWANDTE CHEMIE, vol. 109, no. 5, 1997, pages 543-4, XP002095720 cited in the application see page 544, scheme 4, page 544	1-7.17	
A	scheme 3, compound 10 see page 543, scheme 2	13
P,X	DE 196 36 343 C (SCHERING AG) 23 October 1997 see scheme 1	1-7
A,P	see scheme 2	13
P,X	DE 197 01 758 A (L. A. WESSJOHANN) 23 July 1998 see page 3, formula Iv and the corresponding definitions in the text	13
P,X	WO 98 08849 A (NOVARTIS AG) 5 March 1998 see claim 2	1-7
X	---	
K. C. NICOLAOU ET AL.: NATURE, vol. 387, no. 6630, 15 May 1997, pages 268-72, XP002095721 cited in the application see figure 1, compound 1; figure 4, compound 2	1-7	
A	see figure 1, compound 6; figure 4, compound 6	13

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INTERNATIONAL SEARCH REPORT

International Application No
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X	ZHEN YANG ET AL.: ANGEWANDTE CHEMIE, vol. 109, no. 1/2, 1997, pages 170-2, XP002095722 cited in the application See page 170, figure 1 See page 170, scheme 1, compound 5 ----	1-7
A	K. C. NICOLAOU ET AL.: ANGEWANDTE CHEMIE, vol. 109, no. 19, 1997, pages 2181-7, XP002095723 cited in the application See page 2181, right-hand column, Compounds 1 and 2 See page 2183, scheme, compounds of formula B	13
P, X	D. SCHINZER ET AL.: CHEMISTRY - A EUROPEAN JOURNAL, vol. 2, no. 11, 1996, pages 1477-82, XP002095724 cited in the application See page 1477, scheme 1; page 1479, scheme 6, compounds 27 and 11 see page 1478, scheme 4; page 1479, scheme 6, compounds 28 and 9	1-7, 17
A	K. TAMAQ ET AL.: JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS, 1988, pages 795-7, XP002095725 see page 796, compound (7)	13, 17
X	K. A. PARKER ET AL.: JOURNAL OF ORGANIC CHEMISTRY, vol. 52, no. 19, 1987, pages 4369-77, XP002095726 see page 4370, scheme II, compound 15	13
X	W. CLARK STILL ET AL.: TETRAHEDRON LETTERS, vol. 21, 1980, pages 1031-4, XP002095727 see page 1033, starting and final products of the second and third reaction equation -----	17, 29

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 98/05064

Additional matter PCT/ISA/210

Claims Nos. 1-7, 9-30

The disclaimer of Claim 1 which refers to R2a and R2b cannot be valid for the claims dependent on Claim 1, as these claims do not contain the values R2a and R2b. For this reason, the already known natural epothilone derivatives are prejudicial as to novelty at least for claims 3 and 4. It is unclear whether Claims 3 and 4 consequently do not represent a subset of Claim 1, rather they overlap with Claim 1 (Claims 2, 5, 6 and 7 also do not refer to the disclaimer); as a result, the desired scope of protection is not clearly defined (Art. 6 PCT).

Several of the compounds which are revealed in publications cited in the search report fall in fact under the scope of Claims 13, 17 or 29 and are thus prejudicial as to novelty; there are however compounds which clearly possess no characteristic structural features of the final products. These claims also do not clearly define the object for which protection is sought (Art. 6 PCT). Basically, Claims 13, 17 and 29 were searched for technical as well as for economic reasons primarily with regard to the possibilities which can actually be utilized to produce the final products and have a minimum mass of structural similarity to the final products.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/05064

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9719086	A	NONE	
DE 4138042	A	NONE	
DE 19636343	C	NONE	
DE 19701758	A	NONE	
WO 9808849	A	NONE	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/05064

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IPC 6 C07D405/06 C07D417/06 C07D493/04 C07D313/00 C07C49/185
 C07C49/17 C07C59/185 C07C69/66 C07F7/18 A61K31/335
 A61K31/425 A61K31/44 // (C07D493/04, 313:00, 303:00)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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Fax: (+31-70) 340-3016

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/05064

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"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
9 March 1999	22/03/1999
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentstaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx. 31 651 eoo m. Fax: (+31-70) 340-3016	Authorized officer Hass, C

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/05064

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
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P,X	K. C. NICOLAOU ET AL.: ANGEWANDTE CHEMIE, vol. 109, no. 19, 1997, pages 2181-7, XP002095723 cited in the application See page 2181, right-hand column, Compounds 1 and 2 See page 2183, scheme, compounds of formula B	1-7 13
X	D. SCHINZER ET AL.: CHEMISTRY - A EUROPEAN JOURNAL, vol. 2, no. 11, 1996, pages 1477-82, XP002095724 cited in the application See page 1477, scheme 1; page 1479, scheme 6, compounds 27 and 11 see page 1478, scheme 4; page 1479, scheme 6, compounds 28 and 9	1-7, 17
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X	K. A. PARKER ET AL.: JOURNAL OF ORGANIC CHEMISTRY, vol. 52, no. 19, 1987, pages 4369-77, XP002095726 see page 4370, scheme II, compound 15	13
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International Application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9719086	A	NONE	
DE 4138042	A	NONE	
DE 19636343	C	NONE	
DE 19701758	A	NONE	
WO 9808849	A	NONE	

**VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT
IM GEBIET DES PATENTWESENS**

PCT

INTERNATIONALER RECHERCHENBERICHT

(Artikel 18 sowie Regeln 43 und 44 PCT)

Aktenzeichen des Anmelders oder Anwalts 51516AW0M1XX	WEITERES VORGEHEN	siehe Mitteilung über die Übermittlung des internationalen Recherchenberichts (Formblatt PCT/ISA/220) sowie, soweit zutreffend, nachstehender Punkt 5
Internationales Aktenzeichen PCT/EP 98/ 05064	Internationales Anmeldedatum (Tag/Monat/Jahr) 10/08/1998	(Frühestes) Prioritätsdatum (Tag/Monat/Jahr) 09/08/1997
Anmelder SCHERING AKTIENGESELLSCHAFT et al.		

Dieser internationale Recherchenbericht wurde von der Internationalen Recherchenbehörde erstellt und wird dem Anmelder gemäß Artikel 18 übermittelt. Eine Kopie wird dem Internationalen Büro übermittelt.

Dieser internationale Recherchenbericht umfaßt insgesamt 6 Blätter.

Darüber hinaus liegt ihm jeweils eine Kopie der in diesem Bericht genannten Unterlagen zum Stand der Technik bei.

1. Grundlage des Berichts

- a. Hinsichtlich der **Sprache** ist die internationale Recherche auf der Grundlage der internationalen Anmeldung in der Sprache durchgeführt worden, in der sie eingereicht wurde, sofern unter diesem Punkt nichts anderes angegeben ist.
- Die internationale Recherche ist auf der Grundlage einer bei der Behörde eingereichten Übersetzung der internationalen Anmeldung (Regel 23.1 b)) durchgeführt worden.
- b. Hinsichtlich der in der internationalen Anmeldung offenbarten **Nukleotid- und/oder Aminosäuresequenz** ist die internationale Recherche auf der Grundlage des Sequenzprotokolls durchgeführt worden, das
- in der internationalen Anmeldung in Schriftlicher Form enthalten ist.
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 - bei der Behörde nachträglich in computerlesbarer Form eingereicht worden ist.
 - Die Erklärung, daß das nachträglich eingereichte schriftliche Sequenzprotokoll nicht über den Offenbarungsgehalt der internationalen Anmeldung im Anmeldezeitpunkt hinausgeht, wurde vorgelegt.
 - Die Erklärung, daß die in computerlesbarer Form erfaßten Informationen dem schriftlichen Sequenzprotokoll entsprechen, wurde vorgelegt.

2. **Bestimmte Ansprüche haben sich als nicht recherchierbar erwiesen** (siehe Feld I).

3. **Mangelnde Einheitlichkeit der Erfindung** (siehe Feld II).

4. Hinsichtlich der Bezeichnung der Erfindung

- wird der vom Anmelder eingereichte Wortlaut genehmigt.
- wurde der Wortlaut von der Behörde wie folgt festgesetzt:

5. Hinsichtlich der Zusammenfassung

- wird der vom Anmelder eingereichte Wortlaut genehmigt.
- wurde der Wortlaut nach Regel 38.2b).in der in Feld III angegebenen Fassung von der Behörde festgesetzt. Der Anmelder kann der Behörde innerhalb eines Monats nach dem Datum der Absendung dieses internationalen Recherchenberichts eine Stellungnahme vorlegen.

6. Folgende Abbildung der Zeichnungen ist mit der Zusammenfassung zu veröffentlichen: Abb. Nr. _____

- wie vom Anmelder vorgeschlagen
- weil der Anmelder selbst keine Abbildung vorgeschlagen hat.
- weil diese Abbildung die Erfindung besser kennzeichnet.

keine der Abb.

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen

PCT/EP 98/05064

Feld I Bemerkungen zu den Ansprüchen, die sich als nicht recherchierbar erwiesen haben (Fortsetzung von Punkt 2 auf Blatt 1)

Gemäß Artikel 17(2a) wurde aus folgenden Gründen für bestimmte Ansprüche kein Recherchenbericht erstellt:

1. Ansprüche Nr.
weil sie sich auf Gegenstände beziehen, zu deren Recherche die Behörde nicht verpflichtet ist, nämlich

 2. Ansprüche Nr.
weil sie sich auf Teile der internationalen Anmeldung beziehen, die den vorgeschriebenen Anforderungen so wenig entsprechen, daß eine sinnvolle internationale Recherche nicht durchgeführt werden kann, nämlich

 3. Ansprüche Nr.
weil es sich dabei um abhängige Ansprüche handelt, die nicht entsprechend Satz 2 und 3 der Regel 6.4 a) abgefaßt sind.

Feld II Bemerkungen bei mangelnder Einheitlichkeit der Erfindung (Fortsetzung von Punkt 3 auf Blatt 1)

Die internationale Recherchenbehörde hat festgestellt, daß diese internationale Anmeldung mehrere Erfindungen enthält:

1. Da der Anmelder alle erforderlichen zusätzlichen Recherchengebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht auf alle recherchierbaren Ansprüche.
 2. Da für alle recherchierbaren Ansprüche die Recherche ohne einen Arbeitsaufwand durchgeführt werden konnte, der eine zusätzliche Recherchengebühr gerechtfertigt hätte, hat die Behörde nicht zur Zahlung einer solchen Gebühr aufgefordert.
 3. Da der Anmelder nur einige der erforderlichen zusätzlichen Recherchengebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht nur auf die Ansprüche, für die Gebühren entrichtet worden sind, nämlich auf die Ansprüche-Nr.
 4. Der Anmelder hat die erforderlichen zusätzlichen Recherchengebühren nicht rechtzeitig entrichtet. Der internationale Recherchenbericht beschränkt sich daher auf die in den Ansprüchen zuerst erwähnte Erfindung; diese ist in folgenden Ansprüchen erfaßt:

Bemerkungen hinsichtlich eines Widerspruchs

- Die zusätzlichen Gebühren wurden vom Anmelder unter Widerspruch gezahlt.
 Die Zahlung zusätzlicher Recherchengebühren erfolgte ohne Widerspruch.

WEITERE ANGABEN

PCT/ISA/ 210

Ansprüche Nr.: 1-7,9-30

Der Disclaimer des Anspruchs 1, der sich auf R2a und R2b bezieht, kann nicht für die von Anspruch 1 abhängigen Ansprüche gelten, da diese die Größen R2a und R2b nicht enthalten. Daher sind die bereits bekannten natürlichen Epothilon-Derivate neuheitsschädlich zumindest für die Ansprüche 3 und 4.. Unklarheit ergibt sich daraus, dass die Ansprüche 3 und 4 folglich nicht eine Teilmenge des Anspruchs 1 darstellen, sondern mit ihm überlappen (die Ansprüche 2, 5 6 und 7 erwähnen den Disclaimer auch nicht); dadurch ist der gewünschte Schutzmfang nicht klar umrissen (Art. 6 PCT).

Einige der im Recherchenbericht genannten Druckschriften offenbaren Verbindungen, die zwar unter den Umfang der Ansprüche 13, 17 oder 29 fallen und die daher neuheitsschädlich sind; es sind jedoch Verbindungen, die offensichtlich kein charakteristisches Strukturmerkmal der Endprodukte besitzen. Auch diese Ansprüche umreissen daher nicht klar den Gegenstand, für den Schutz gewünscht wird (Art. 6 PCT). Im wesentlichen wurden deshalb die Ansprüche 13, 17 und 29 aus technischen, aber auch aus ökonomischen Gründen hauptsächlich im Hinblick auf die Möglichkeiten recherchiert, die tatsächlich zur Herstellung der Endprodukte verwendet werden können und ein Mindestmass an struktureller Nähe zu den Endprodukten aufweisen.

A. KLASIFIZIERUNG DES ANMELDUNGSGEGENSTANDES

IPK 6 C07D405/06 C07D417/06 C07D493/04 C07D313/00 C07C49/185
 C07C49/17 C07C59/185 C07C69/66 C07F7/18 A61K31/335
 A61K31/425 A61K31/44 // (C07D493/04, 313:00, 303:00)

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierte Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)

IPK 6 C07D C07C C07F

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	WO 97 19086 A (GESELLSCHAFT FÜR BIOTECHNOLOGISCHE FORSCHUNG MBH) 29. Mai 1997 in der Anmeldung erwähnt siehe Seite 7, letzter Absatz siehe Ansprüche 4,13 ----	1-7,10, 11
X	DE 41 38 042 A (GESELLSCHAFT FÜR BIOTECHNOLOGISCHE FORSCHUNG MBH) 27. Mai 1993 siehe Ansprüche 1,2,8 ----	1-7,10, 11 -/-

Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

Siehe Anhang Patentfamilie

* Besondere Kategorien von angegebenen Veröffentlichungen :

"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist

"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldeatum veröffentlicht worden ist

"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)

"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht

"P" Veröffentlichung, die vor dem internationalem Anmeldeatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist

"T" Spätere Veröffentlichung, die nach dem internationalen Anmeldeatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist

"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erforderlicher Tätigkeit beruhend betrachtet werden

"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erforderlicher Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist

"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der internationalen Recherche

Absendedatum des internationalen Recherchenberichts

9. März 1999

22/03/1999

Name und Postanschrift der Internationalen Recherchenbehörde
 Europäisches Patentamt, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Bevollmächtigter Bediensteter

Hass, C

INTERNATIONALER FORSCHENBERICHT

Internationales Aktenzeichen

PCT/EP 98/05064

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
P,X	K. C. NICOLAOU ET AL.: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, Bd. 119, Nr. 34, 1997, Seiten 7974-91, XP002095719 in der Anmeldung erwähnt siehe Schema 1, Verbindungen 1 und 2; Schema 2, Verbindung 20 ---	1-7,13
P,X	K. C. NICOLAOU: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, Bd. 119, Nr. 34, 1997, Seiten 7960-73, XP002064442 in der Anmeldung erwähnt siehe Seite 7960, Verbindungen 1 und 2 siehe Seite 7961, Schema 1, Verbindung 8	1-7
A		13
X	D. SCHINZER ET AL.: ANGEWANDTE CHEMIE, Bd. 109, Nr. 5, 1997, Seiten 543-4, XP002095720 in der Anmeldung erwähnt siehe Seite 544, Schema 4; Seite 544, Schema 3, Verbindung 10 siehe Seite 543, Schema 2	1-7,17
A		13
P,X	DE 196 36 343 C (SCHERING AG) 23. Oktober 1997 siehe Schema 1	1-7
A,P	siehe Schema 2	13
P,X	DE 197 01 758 A (L. A. WESSJOHANN) 23. Juli 1998 siehe Seite 3, Formel Iv und die entsprechenden Definitionen im Text ---	13
P,X	WO 98 08849 A (NOVARTIS AG) 5. März 1998 siehe Anspruch 2 ---	1-7
X	K. C. NICOLAOU ET AL.: NATURE, Bd. 387, Nr. 6630, 15. Mai 1997, Seiten 268-72, XP002095721 in der Anmeldung erwähnt siehe Figur 1, Verbindung 1; Figur 4, Verbindung 2 siehe Figur 1, Verbindung 6; Figur 4, Verbindung 6	1-7
A		13

	-/-	

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	ZHEN YANG ET AL.: ANGEWANDTE CHEMIE, Bd. 109, Nr. 1/2, 1997, Seiten 170-2, XP002095722 in der Anmeldung erwähnt siehe Seite 170, Abb. 1 siehe Seite 170, Schema 1, Verbindung 5	1-7
A	---	13
P, X	K. C. NICOLAOU ET AL.: ANGEWANDTE CHEMIE, Bd. 109, Nr. 19, 1997, Seiten 2181-7, XP002095723 in der Anmeldung erwähnt siehe Seite 2181, rechte Spalte, Verbindungen 1 und 2 siehe Seite 2183, Schema, Verbindungen der Formel B	1-7
A	---	13
X	D. SCHINZER ET AL.: CHEMISTRY - A EUROPEAN JOURNAL, Bd. 2, Nr. 11, 1996, Seiten 1477-82, XP002095724 in der Anmeldung erwähnt siehe Seite 1477, Schema 1; Seite 1479, Schema 6, Verbindungen 27 und 11 siehe Seite 1478, Schema 4; Seite 1479, Schema 6, Verbindungen 28 und 9	1-7, 17
A	---	13, 17
X	K. TAMAO ET AL.: JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS, 1988, Seiten 795-7, XP002095725 siehe Seite 796, Verbindung (7)	13
X	---	13
X	K. A. PARKER ET AL.: JOURNAL OF ORGANIC CHEMISTRY, Bd. 52, Nr. 19, 1987, Seiten 4369-77, XP002095726 siehe Seite 4370, Schema II, Verbindung 15	13
X	---	13
X	W. CLARK STILL ET AL.: TETRAHEDRON LETTERS, Bd. 21, 1980, Seiten 1031-4, XP002095727 siehe Seite 1033, Ausgangs- und Endprodukte der zweiten und dritten Reaktionsgleichung	17, 29

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/05064

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9719086	A	NONE	
DE 4138042	A	NONE	
DE 19636343	C	NONE	
DE 19701758	A	NONE	
WO 9808849	A	NONE	

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

**NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT**

(PCT Administrative Instructions, Section 411)

To:

SCHERING AKTIENGESELLSCHAFT
Müllerstrasse 178
D-13353 Berlin
ALLEMAGNE

Date of mailing (day/month/year) 22 October 1998 (22.10.98)
--

Applicant's or agent's file reference 51516AWOM1XX	IMPORTANT NOTIFICATION
International application No. PCT/EP98/05064	International filing date (day/month/year) 10 August 1998 (10.08.98)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 09 August 1997 (09.08.97)
Applicant SCHERING AKTIENGESELLSCHAFT et al	

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
09 Augu 1997 (09.08.97)	197 35 574.9	DE	21 Octo 1998 (21.10.98)
09 Augu 1997 (09.08.97)	197 35 575.7	DE	21 Octo 1998 (21.10.98)
09 Augu 1997 (09.08.97)	197 35 578.1	DE	21 Octo 1998 (21.10.98)
24 Octo 1997 (24.10.97)	197 48 928.1	DE	21 Octo 1998 (21.10.98)
31 Octo 1997 (31.10.97)	197 49 717.9	DE	21 Octo 1998 (21.10.98)
13 Nove 1997 (13.11.97)	197 51 200.3	DE	21 Octo 1998 (21.10.98)
20 Marc 1998 (20.03.98)	198 13 821.0	DE	21 Octo 1998 (21.10.98)

The International Bureau f WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer Kari Huynh Khuong Telephone No. (41-22) 338.83.38
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PATENT COOPERATION TREATY

PCT

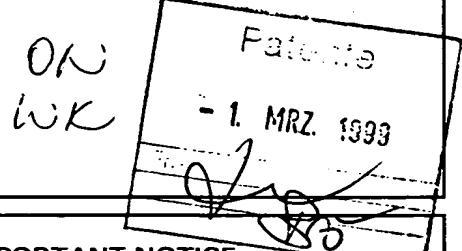
NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

SCHERING AKTIENGESELLSCHAFT
Müllerstrasse 178
D-13353 Berlin
ALLEMAGNE

**IMPORTANT NOTICE**

Date of mailing (day/month/year) 18 February 1999 (18.02.99)		
Applicant's or agent's file reference 51516AWOM1XX 00 + P		
International application No. PCT/EP98/05064	International filing date (day/month/year) 10 August 1998 (10.08.98)	Priority date (day/month/year) 09 August 1997 (09.08.97)
Applicant SCHERING AKTIENGESELLSCHAFT et al		

- Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
AU, BR, CN, EP, IL, JP, KP, KR, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

- The following designated Offices have waived the requirement for such a communication at this time:
AL, AM, AP, AT, AZ, BA, BB, BG, BY, CA, CH, CU, CZ, DK, EA, EE, ES, FI, GB, GE, GH, GM, HU, ID, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, OA, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW
The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).
- Enclosed with this Notice is a copy of the international application as published by the International Bureau on 18 February 1999 (18.02.99) under No. WO 99/07692

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
---	------------------------------------

Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38
---------------------------------	---------------------------------

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT**INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION**

(PCT Rule 61.3)

To:	ON WK	17. MAI 1999
SCHERING AKTIENGESELLSCHAFT		
Müllerstrasse 178		
D-13353 Berlin		
ALLEMAGNE		

[Signature]

Date of mailing (day/month/year) 04 May 1999 (04.05.99)
--

Applicant's or agent's file reference 51516AWOM1XX 00 + P
--

IMPORTANT INFORMATION

International application No. PCT/EP98/05064	International filing date (day/month/year) 10 August 1998 (10.08.98)	Priority date (day/month/year) 09 August 1997 (09.08.97)
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Applicant SCHERING AKTIENGESELLSCHAFT et al
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1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

AP :GH,GM,KE,LS,MW,SD,SZ,UG,ZW

EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE

National :AU,BG,BR,CA,CN,CZ,GB,IL,JP,KP,KR,MN,NO,NZ,PL,RO,RU,SE,SK,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM

OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG

National :AL,AM,AT,AZ,BA,BB,BY,CH,CU,DK,EE,ES,FI,GE,GH,GM,HU,ID,IS,KE,KG,
KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MW,MX,PT,SD,SG,SI,SL,TJ,TM,TR,TT,UA,UG,
UZ,VN,YU,ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

A. Karkachi

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION
(PCT Rule 61.2)

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 04 May 1999 (04.05.99)	United States Patent and Trademark Office (Box PCT) Crystal Plaza 2 Washington, DC 20231 ÉTATS-UNIS D'AMÉRIQUE
International application No. PCT/EP98/05064	Applicant's or agent's file reference 51516AWOM1XX
International filing date (day/month/year) 10 August 1998 (10.08.98)	Priority date (day/month/year) 09 August 1997 (09.08.97)
Applicant KLAR, Ulrich et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

05 March 1999 (05.03.99)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer A. Karkachi Telephone No.: (41-22) 338.83.38
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M-H

5292
PATENT COOPERATION TREATY

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Translation

SOLC

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 51516AWOM1XX	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP98/05064	International filing date (<i>day/month/year</i>) 10 August 1998 (10.08.1998)	Priority date (<i>day/month/year</i>) 09 August 1997 (09.08.1997)
International Patent Classification (IPC) or national classification and IPC C07D 405/06, 417/06, 493/04, 313/00, C07C 49/185, 49/17, 59/185, 69/66, C07F 7/18, A61K 31/335, 31/425, 31/44 // , ,		
Applicant SCHERING AKTIENGESELLSCHAFT		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 13 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

Date of submission of the demand 05 March 1999 (05.03.1999)	Date of completion of this report 23 December 1999 (23.12.1999)
Name and mailing address of the IPEA/EP European Patent Office D-80298 Munich, Germany Facsimile No. 49-89-2399-4465	Authorized officer Telephone No. 49-89-2399-0

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

PCT/EP98/05064

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

 the international application as originally filed. the description, pages 1 - 162, as originally filed,

pages _____, filed with the demand,

pages _____, filed with the letter of _____,

pages _____, filed with the letter of _____.

 the claims, Nos. 1 - 13, as originally filed,

Nos. _____, as amended under Article 19,

Nos. _____, filed with the demand,

Nos. _____, filed with the letter of _____,

Nos. _____, filed with the letter of _____.

 the drawings, sheets/fig _____, as originally filed,

sheets/fig _____, filed with the demand,

sheets/fig _____, filed with the letter of _____,

sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

 the description, pages _____ the claims, Nos. _____ the drawings, sheets/fig _____

3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- the entire international application.
 claims Nos. 3, 4, 7

because:

- the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international preliminary examination (*specify*):

- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 3, 4, 7 are so unclear that no meaningful opinion could be formed (*specify*):

See Supplemental Box

- the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.
 no international search report has been established for said claims Nos. _____

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III.

Compounds of the formula according to Claims 1, 2, 5, 6, and 8 differ from the epothilones A and B (cf. D2 and D3), epothilones C and D (D1), and the epothilone derivatives (cf. Claims 1 and 4 according to D1) with the proviso that R^{2a} or R^{2b} cannot be hydrogen/methyl if D-E is CH₂CH₂ or Y represents a oxygen atom. Furthermore, D4 and D6 disclose that epothilones A and B interact with tubulin and have an effect on cancer cells, and D1 discloses that epothilones C and D and the epothilone derivatives have an anti-tumor effect.

With regard to this prior art (D1, D2, or D3), there are various structural features in relation to epothilones A-D or the further epothilone derivatives according to D1, which have no technical relationship. Therefore, different inventions/groups (cf. A-D below) exist, which are not connected such that they form a single inventive concept.

Similar considerations apply to Claims 9-11.

b) The method according to Claim 12 leads to compounds which are not claimed in Claim 13 or not known, so that two different objectives exist with regard to these claims, and these objectives do not form a single inventive concept:

i) providing new intermediate products and ii) providing a new method for producing at least partially known compounds (cf. D2, Figure 4, Compound 6; D4, Figure 1, Compound 5; D5, Compound 7; D6, Figure II, Compound 15).

INTERNATIONAL PRELIMINARY EXAMINATION REPORTInternational application No.
PCT/EP 98/05064**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III.

Providing new intermediate products can only show unity with the inventive concepts A-D (cf. below), if these concepts contribute to the distinguishing feature of the end product.

There are no compounds according to Claim 13 which show unity with the inventive concepts C and D (they do not contribute to the distinguishing feature).

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- restricted the claims.
- paid additional fees.
- paid additional fees under protest.
- neither restricted nor paid additional fees.

2. This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- complied with.
- not complied with for the following reasons:

See Supplemental Box

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- all parts.
- the parts relating to claims Nos. _____ 1, 2, 5, 8 - 13 _____

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.

The different inventions/groups of inventions are:

- A) Compounds of formula I, wherein Y is oxygen and the structural difference occurs in group R^{2a} or R^{2b}, and R^{2a} and R^{2b} are **not** simultaneously hydrogen (cf. the corresponding H/Me groups according to D1, D4, and D6): cf. Claims 1 (partially), 2 (partially), 5 (partially), 6 (partially), Claim 8, (partially), 9-12 (partially), and 13 (partially).
- B) Compounds of formula I, wherein Y is oxygen and R^{2a} or R^{2b} are simultaneously hydrogen (cf. the corresponding H/Me groups according to D1, D4, and D6): cf. the present Claims 1 (partially), 2 (partially), 5 (partially), 6 (partially), 8 (partially) 9-12 (partially), and 13 (partially).
- C) Compounds according to Claims 1-8, wherein Y represents two hydrogen atoms: cf. the present Claims 1 (partially), 2 (partially), 5 (partially), 6 (partially), 8 (partially), 9-12 (partially).
- D) Claim 8 (in part) - the distinguishing feature is not shown by Y or R^{2a} or R^{2b} (cf. for example, 1S,3S(E),7S,10R,11S,12S,16R)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-((4-pyridyl)ethenyl)-4,17-dioxabicyclo[4.1.0]heptadecan-5,9-dion).

Therefore, the required unity of invention (PCT Rule 13.1) is not established since a technical relationship within the meaning of PCT Rule 13.2 involving one or more of the same or corresponding special technical features does not exist between the subjects of the aforementioned groups of

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.

compounds.

There are further objections in terms of unity with regard to invention D (cf. Claim 8 (in part) - cf. Box V) since various features of the epothilones A-D are disclosed by the closest prior art (D1-D3):

- a) Group X - a (3-pyridyl)ethenyl group instead of a 2-methyl-4-thiazolyl)ethenyl group
- b) Group R^{4a}/R^{4b} - a CF₃ or trimethylene instead of a CH₃ group
- c) Group D-E, which forms a double-bond or a triple-bond
- d) Group R⁵ is a CF₃ or a pentafluoroethyl group.

These features are not so related as to form a single inventive concept, and thus, four further inventions/groups exist in Claim 8.

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	<u>1, 2, 5, 6, 8-12</u>	YES
	Claims	<u>13</u>	NO
Inventive step (IS)	Claims		YES
	Claims	<u>1, 2, 5, 6, 8-13</u>	NO
Industrial applicability (IA)	Claims	<u>1, 2, 5, 6, 8-13</u>	YES
	Claims		NO

2. Citations and explanations

This report makes reference to the following documents:

D1: WO 97 19086 A (Gesellschaft für Biotechnologische Forschung MBH) May 29, 1997, mentioned in the application

D2: K.C. Nicolaou et al.: Nature, vol. 387, no. 6630, May 15, 1997, pages 268-72, XP002095721, mentioned in the application

D3: D. Schinzer et al.: Chemistry - A European Journal, vol. 2, no. 11, 1996, pages 1477-82, XP002095724, mentioned in the application

D4: Zhen Yang et al.: Angewandte Chemie, vol. 109, no. 1/2, 1997, pages 170-2, XP002095722, mentioned in the application

D5: K. Tamao et al.: Journal of the Chemical Society, Chemical Communications, 1988, pages 795-7, XP002095725

D6: K. A. Parker et al.: Journal of Organic Chemistry, vol. 52, no. 19, 1987, pages 4369-77, XP002095726

D7: (not relevant for inventions A-D)

D8: D. Schinzer et al.: Angewandte Chemie, vol. 109, no. 5, 1997, pages 543-4, XP002095720, mentioned in the application

D9: DE 41 38 042 A (Gesellschaft für Biotechnologische

Forschung) May 27, 1993

Invention A

Compounds of formula I, wherein Y is oxygen, and R^{2a} and R^{2b} are not simultaneously hydrogen.

Novelty

This report was drawn up under the assumption that, with regard to the proviso "if D-E represents CH₂-CH₂ or Y represents an oxygen atom, then R^{2a}/R^{2b} cannot be hydrogen/methyl", the following meanings of R^{2a} and R^{2b} are intended in the disclaimer: R^{2a} is hydrogen, R^{2b} is methyl, or R^{2a} is methyl and R^{2b} is hydrogen. The compounds of Claim 1 appear to be novel over D1-D4, D8, and D9 owing to this proviso (cf. however, Box V, Point 1).

Claim 13 is novel over formula 6 according to D2, formulas 9 and 27, formula 5 according to D4 (owing to the disclaimer), and formula 10 according to D8.

Inventive Step

D2 and D3 are considered the closest prior art since these documents disclose very similar compounds, which interact with tubulin and have an effect on cancer cells.

Given the trivial structural differences between the claimed compounds and the compounds known from D2 or D3, the newly claimed compounds offer alternatives to the compounds known from D2 and D3 which are obvious to a person skilled in the art, for example, compounds in which a methyl group is replaced by an ethyl group.

The problem on which the application is based could therefore be that of providing further epothilones which have an unexpected effect in relation to the most similar compounds of the prior art.

Even if the compounds of formula I (invention A) show an unexpected effect, they do not appear to involve an inventive step.

Invention B

Y is oxygen and R^{2a} and R^{2b} are simultaneously hydrogen.

Novelty

The compounds of formula I according to invention B differ from the compounds according to D1-D4, D8 and D9 by the fact that the 6-position (cf. numbering of the epothilones in D1) is unsubstituted, i.e. R^{2a} and R^{2b} are simultaneously hydrogen, whereas in D1-D4, D8, and D9, the 6-position is substituted by a methyl group.

Compound 7 according to D5, and compound 15 according to D6 are prejudicial to the novelty of the compounds of formula A' according to Claim 13.

Inventive Step

Given the trivial structural differences between the claimed compounds and the compounds known from D2 or D3 (closest prior art), the newly claimed compounds offer alternatives to the compounds known from D2 and D3 which are obvious to a person skilled in the art.

This view is confirmed by the scope of Claim 1, wherein the structural differences between the claimed compounds

and the examples are much larger than the differences between the claimed compounds and epothilones A and B.

Invention C

Y represents two hydrogen atoms.

Novelty

The compounds according to formula I differ from the compounds according to D1-D4, D8 and D9 in that Y represents two hydrogen atoms, whereas the corresponding group according to D1-D4, D8, and D9 is oxygen.

Inventive Step

Given the trivial structural differences between the claimed compounds and the compounds known from D2 or D3 (closest prior art), the newly claimed compounds offer alternatives to the compounds known from D2 and D3 which are obvious to a person skilled in the art.

Invention D

The distinguishing feature is not shown by Y or R^{2a} or R^{2b}.

Novelty

These compounds of formula I appear to be novel over D1-D4, D8, and D9 (cf. the features in Box IV).

Inventive Step

An inventive step can be recognized for the compounds according to Claim 8, said compounds being substituted by

the 1-methyl-2-(pyridyl)ethenyl group, since this group does not appear to be an obvious alternative to the 1-methyl-2-(2-methyl-4-thiazolyl)ethenyl group according to D1-D3.

Claim 8 does, however, contain compounds that are obvious.

The other compounds (cf. b)-d)) in Box IV, appear to be obvious (cf. for example, replacing a CH₃ group with a CF₃ group).

Scope of Claims 1, 2, 5, and 6

a) Claims 1, 2, 5, and 6 are not allowed since the definitions of the residues contain largely unspecified expressions, such as "aryl", "all of which can be substituted", "protective group". These expressions include possibilities that the problem addressed by the application cannot solve.

b) An objection with regard to the scope of the claims could be raised in the regional phase for the following reasons:

It is unclear which of the examples were tested, and thus a final examination of the scope does not appear to be possible. The residues indicated by the applicants in Claims 1, 2, 5, and 6 go beyond what can be considered as reasonable alternatives to the examples, even if they had been tested (with regard to the generally accepted definition of structure and activity).

INTERNATIONAL PRELIMINARY EXAMINATION REPORT**VI. Certain documents cited****1. Certain published documents (Rule 70.10)**

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
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See Supplemental Box**2. Non-written disclosures (Rule 70.9)**

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)
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Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: VI.

Certain published documents (PCT Rule 70.10)

- D10: K. C. Nicolaou et al.: Journal of the American Chemical Society, vol. 119, no. 34, 1997, pages 7974-91, XP002095719, mentioned in the application
- D11: K. C. Nicolaou: Journal of the American Chemical Society, vol. 119, no. 34, 1997, pages 7960-73, XP002064442, mentioned in the application
- D12: DE 196 36 343 C (Schering AG) October 23, 1997
- D13: DE 197 01 758 A (L. A. Wessjohann) July 23, 1998
- D14: WO 98 08849 A (Novartis AG) March 5, 1998
- D15: K. C. Nicolaou et al.: Angewandte Chemie, vol. 109, no. 19, 1997, pages 2181-7, XP002095723, mentioned in the application
- D16: WO 98 25929 A (Novartis AG) June 18, 1998
- D17: WO 99 02514 A (Bristol Mayers Squibb Company) January 21, 1999
- D18: WO 99 01124 A (Sloan Kettering Institute for Cancer Research) January 14, 1999

This report is based on the assumption that all claims enjoy priority of the filing date of the priority document. If this does not prove correct at a later time, the aforementioned D14 and D15 could become relevant for assessing novelty and inventive step, and D15 and D18 for novelty.

Furthermore, the filing date of D14 is earlier than the priority date of the application and the priorities of D16-D18 are earlier than the priority date of the application.

INTERNATIONAL PRELIMINARY EXAMINATION REPORTInternational application No.
PCT/EP 98/05064**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

Contrary to the requirements of PCT Rule 5.1(a)(ii), neither the relevant prior art disclosed in D9, D12, D13, and D14 nor these documents themselves have been indicated in the description.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. It is not clear whether the proviso in Claim 1, "wherein R^{2a}/R^{2b} cannot be hydrogen/methyl if -D-E represents -CH₂-CH₂ or Y represents an oxygen atom", also includes a situation in which R^{2a} is methyl and R^{2b} is hydrogen. If this is not the case, then D1-D4, D8, and D9 would be prejudicial to the novelty of Claims 1, 2, 5, and 6.
2. The definitions R^{1a}, R^{1b}, R^{2a}, R^{2c}, R³, R⁴, R⁵, R⁸, R⁹, R¹⁰, R¹¹, R¹², R^{13b}, R^{14b}, R^{15a}, R^{15b}, R¹⁷, and R²³ in Claims 1 are unclear in light of the description, which discloses that the alkyl groups are perfluorinated or substituted ... by 1-5 halogen atoms (page 6, lines 5-8).
3. The term "aryl" in Claim 1 is unclear in light of the description (page 6, lines 9-16) since this term usually does not include heterocycles or substituted aryl groups.

Similar considerations apply to the term "aralkyl" in Claim 1 (cf. page 6, lines 9-24).

4. It appears that the compounds according to Claim 1, which are substituted by a protective group, are not considered to be active compounds, but intermediate products. Therefore, there is a contradiction with Claims 10 and 11, which concern pharmaceutical preparations and the use of the compounds of general formula I according to Claim 1 for producing drugs.

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VIII. Certain observations on the international application

Furthermore, the term "protective group" is unclear since an attempt is made to define the invention by the result to be achieved using this term. Whether a group is understood as a protective group depends also on other conditions (for example, on reaction conditions, which are not at all indicated in Claim 1), and thus, said term leads to a further lack of clarity.

With regard to the subject matter of Claim 1, it should be noted that two independent claims should be claimed (active compounds and intermediate products).

5. Claims 12 and 13 are unclear with regard to Claim 9 since the substituents are numbered differently for the compounds of formula A and A'.
6. Claim 9 appears to be unclear since it does not contain all of the features essential for the method (PCT Article 6 and PCT Rule 6.3(b)).